Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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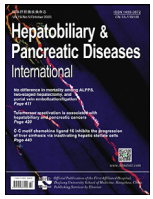

Editorial

Liver injury in COVID-19: What do we know now?

Hua-Yu Yang[#], Bao Jin[#], Yi-Lei Mao[*]

Department of Liver Surgery, Peking Union Medical College (PUMC) Hospital, PUMC & Chinese Academy of Medical Sciences (CAMS), Beijing 100730, China

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become a global pandemic. Several large cohort studies have reported liver injury in COVID-19 patients. Here, we reviewed the manifestations and causes of liver injury in COVID-19 patients and the effects of liver injury on the clinical outcomes based on the published literature.

Common manifestations of liver injury in COVID-19 patients generally include elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL). Interestingly, the prevalence of liver injury in COVID-19 patients varies greatly, ranging from 5% to 61% [1]. This wide variability depends on the definition of liver injury, the sample size, the population and ethnicity in different studies. Most recently, the American Gastroenterological Association (AGA) Institute performed a systematic review and meta-analysis of international data on liver manifestations of COVID-19 [2]. They found that the pooled prevalence of abnormal ALT, AST, and TBIL was 15.0% (95% CI: 13.6%-16.4%), 15.0% (95% CI: 13.6%-16.5%), and 16.7% (95% CI: 15.0%-18.5%), respectively. Abnormal ALT, AST, and TBIL levels were defined as any value above the upper limit of normal (ULN). Of course, this systematic review also had some limitations, and these data should be interpreted carefully. Many included studies did not report previous liver disease or baseline liver function prior to SARS-CoV-2 infection. However, this systematic review containing international multicenter data may provide more reliable insights regarding the manifestations of liver injury. Among COVID-19 patients with liver injury, more than 60% of patients had mild liver injury (1 time ULN $<$ ALT $<$ 2 times ULN); about 30% of patients had moderate liver injury (2 times ULN $<$ ALT $<$ 5 times ULN); and less than 10% of patients had severe liver injury (ALT $>$ 5 times ULN) [3,4]. Similarly, previous liver disease and baseline liver function may have affected the results. In addition, severe COVID-19 patients seem to be more prone to severe liver injury.

There are many causes of liver damage in patients with COVID-19, such as SARS-CoV-2 direct infection, drug toxicity, and the inflammatory storm. Firstly, SARS-CoV-2 may directly damage the liver. There is evidence that SARS-CoV-2 may bind to the angiotensin-converting enzyme 2 (ACE2) receptor in humans. A recent study showed that ACE2 receptors are abundantly expressed in biliary and liver epithelial cells, suggesting that the liver is a potential target for infection [5]. Wang et al. [6] identified typical SARS-CoV-2 particles characterized by a spike structure in the cytoplasm of hepatocytes in two COVID-19 cases. They found that hepatocytes infected by SARS-CoV-2 showed typical viral infection characteristics, such as conspicuous mitochondrial swelling, endoplasmic reticulum dilatation, and glycogen granule decrease. Secondly, liver toxicity caused by various drugs used during the treatment of COVID-19 is also an important cause of liver damage. Commonly used drugs that may cause liver toxicity include remdesivir, tocilizumab, chloroquine, hydroxychloroquine, and azithromycin [4]. Thirdly, the immune-mediated cytokine storm, hypoxia, and ischemia may also contribute to liver injury in patients with COVID-19 [4]. In addition, some patients may have abnormal liver function before SARS-CoV-2 infection, such as nonalcoholic fatty liver disease (NAFLD) or chronic hepatitis B [7,8]. It is often difficult to differentiate whether the liver damage observed in COVID-19 patients is due to SARS-CoV-2 infection or to other causes. The American Association for the Study of Liver Diseases (AASLD) provides recommendations for the management of COVID-19 patients with liver injury, which may be helpful to clinicians. When liver function tests are stable or improved, they should continue to monitor patients closely. When liver function tests are worsening, other causes of liver damage should be evaluated, liver-toxic drugs should be withdrawn, and liver-protective drugs should be administered [4]. Some drugs, such as remdesivir and tocilizumab, used to treat COVID-19 are hepatotoxic; thus, patients with elevated ALT are often excluded from clinical trials involving these drugs. The AASLD recommends that the presence of abnormal liver biochemistries should not be the contraindication to the use of these drugs unless ALT or AST is more than five times higher than the ULN [4].

Several studies have reported the effect of liver injury and previous liver disease on the outcome of COVID-19 patients [3,9,10]. Phipps et al. [3] found that peak ALT is significantly associated with clinical outcomes. Compared with mild to moderate or no liver injury, patients with severe liver injury have a higher rate of intubation and renal replacement therapy. Moreover, these patients are more likely to be admitted to the intensive care unit and die in hospital. Compared with patients without previous liver disease, the outcome of COVID-19 patients with previous liver disease seems to be worse. Singh et al. [9] studied the impact of pre-existing liver disease on outcomes in a large cohort of COVID-19

* Corresponding author.
E-mail address: pumch-liver@hotmail.com (Y.-L. Mao).
[#] Contributed equally.

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patients. They identified a total of 250 (9%) patients with preexisting liver disease and 2530 (91%) patients without preexisting liver disease across 34 medical centers. Fatty liver disease or nonalcoholic steatohepatitis (42%) was the most common among patients with preexisting liver disease. In this cohort, patients in the preexisting liver disease group had more comorbidities, such as hypertension and diabetes. They found that the risk of hospitalization and death in patients with preexisting liver disease was significantly higher, and the risk remained high even after propensity matching of the two groups [9]. Ji et al. [10] found that COVID-19 patients with NAFLD were more likely to have liver damage and disease progression than patients without NAFLD. There is currently no evidence to indicate whether other types of liver disease can also lead to adverse clinical outcomes in COVID-19 patients, such as viral hepatitis B or C, or autoimmune liver disease.

Considering our current insufficient understanding of liver injury in COVID-19, future research should focus on the mechanism leading to liver injury. Larger international multicenter cohorts are needed to evaluate the clinical features of liver injury and the impact of liver injury on outcomes in COVID-19 patients.

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Ethical approval

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Competing interest

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